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Maternal and Paternal Infertility Disorders and Treatments and Autism Spectrum Disorder: Findings from the Study to Explore Early Development

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Abstract

Previous studies of associations between ASD and conception using assisted reproductive technology (ART) are inconsistent and few studies have examined associations with other infertility treatments or infertility disorders. We examined associations between ASD and maternal/paternal infertility disorders and numerous maternal treatments among 1538 mother–child pairs in the Study to Explore Early Development, a population-based case-control study. ASD was associated with any female infertility diagnosis and several specific diagnoses: blocked tubes, endometriosis, uterine-factor infertility, and polycystic ovarian syndrome. Stratified analyses suggested associations were limited to/much stronger among second or later births. The

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findings were not explained by sociodemographic factors such as maternal age or education or multiple or pre-term birth. ASD was not associated with ART or non-ART infertility treatments.

Keywords

Autism spectrum disorder; Neurodevelopmental disorders; Infertility; Reproductive techniques; assisted; Ovulation induction; Epidemiology

Introduction

The U.S. prevalence of autism spectrum disorder (ASD) in children is estimated at 1–2% (Christensen et al. 2016; Blumberg et al. 2013). While much remains unknown about the etiology of ASD, epidemiologic studies suggest that in addition to genetics, ASD is associated with maternal health conditions prior to pregnancy, such as diabetes and autoimmune disorders, and maternal complications and exposures during pregnancy (Ornoy et al. 2016; Schieve et al. 2011). Further, neurobiological and clinical research indicates that children with ASD have very early alterations in brain development (i.e. during fetal development) (Young et al. 2016; Arndt et al. 2005; Bauman and Kemper 2005) and that developmental delays are evident as early as infancy in many children eventually diagnosed with ASD (Bolton et al. 2012). Given the importance of the preconception and prenatal periods in the etiology of ASD, and research suggestive of a link between ASD and in utero hormonal exposure (Wen and Wen 2014), maternal infertility disorders and treatments are of interest as potential ASD risk factors.

Several previous studies have assessed associations between conception with the assistance of infertility treatments and ASD. Most have assessed only the relationship between ASD and assisted reproductive technologies (ARTs) because such data are available from ART registries (Fountain et al. 2015; Sandin et al. 2013; Zachor and Ben Itchach 2011; Knoester et al. 2007; Klemetti et al. 2006). Study findings have been inconsistent. Moreover, in several studies that initially documented associations between conception using ART and ASD in offspring, further investigation revealed that a large component of the association was explained by earlier identification of ASD in children conceived with ARTs (Schieve et al. 2015) and/or the known associations of both ASD and ART with multiple birth and preterm birth among singletons (Fountain et al. 2015; Sandin et al. 2013; Hvidtjorn et al. 2011; Klemetti et al. 2006). Two studies suggested that while ART had little or no association with ASD overall, one specific and particularly intensive ART treatment—intracytoplasmic sperm injection (ICSI)—was possibly associated with ASD and/or intellectual disability (Kissin et al. 2015; Sandin et al. 2013). The few studies that examined a range of both ART and non-ART treatments reported mixed results. One reported no associations between ASD and any of the treatments examined (Lyall et al. 2013). In contrast, two studies found no associations with ART, but significant positive associations between ASD and less invasive treatments—non-ART ovulation induction and/or assisted insemination (Hvidtjorn et al. 2011; Lyall et al. 2012). A possible reason for these seemingly anomalous results is that infertility treatments might not be direct risk factors, but rather indicate associations with underlying maternal or paternal infertility disorders that lead to

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the need for an infertility treatment. However, neither study had sufficiently detailed data to examine the underlying mechanisms for the associations observed.

Only a few studies have directly examined the relationship between ASD and infertility disorders (Grether et al. 2013; Lyall et al. 2012, 2013). While one study initially documented associations between ASD and several infertility indicators, the associations were attenuated and no longer reached statistical significance when limited to singleton births (Grether et al. 2013). However, given that a few risk ratios remained elevated, a possible modest association cannot be ruled out. Two other case-control studies observed no association between ASD and infertility. One was limited by small sample sizes which precluded detailed analyses of specific types of infertility (Lyall et al. 2013). The other had a larger sample size, but had potential methodological shortcomings, particularly in ascertainment of infertility in mothers; further, the findings from this study might have limited generalizability, given the study population was a very select group of predominantly white nurses and their children (Lyall et al. 2012). Other recent studies suggest a positive association with ASD and one specific infertility diagnosis—maternal polycystic ovarian syndrome (PCOS) (Kosidou et al. 2016; Palomba et al. 2012).

Gaps remain in our understanding of whether either infertility disorders or their treatments are associated with ASD. There is a particular need for additional studies of infertility disorders and non-ART treatment. The Study to Explore Early Development (SEED), a multi-site case-control study of ASD risk factors, provided an opportunity for in depth assessments of both infertility disorders and a large range of treatments used by women to assist with both conception and early pregnancy maintenance. SEED offers several advantages to other studies. SEED included detailed data collection of potential ASD risk factors, as well as a rigorous case ascertainment methodology. Cases were identified from multiple educational and clinical sources serving diverse population groups. Case classification was based on in depth standardized in-person developmental assessments administered by research-reliable clinical study staff, rather than on reports of past clinical diagnoses. Exposure ascertainment was based on detailed maternal reproductive histories taken as part of a comprehensive maternal telephone interview administered by interviewers who were extensively trained. Finally, SEED's sample size allowed for more detailed subgroup analyses than several other previous studies.

Methods

SEED Methodology

SEED, a multi-site case-control study funded by the Centers for Disease Control and Prevention (CDC), was implemented in 2007 in six sites located in CA, CO, GA, MD, NC, and PA. Institutional Review Boards at CDC, each study site, and the SEED Data Coordinating Center at Michigan State University approved the SEED protocol. Study methods have been described in detail previously (Schendel et al. 2012) and are summarized here.

Each site enrolled three groups of children—children with ASD (ASD group), children with other non-ASD developmental disabilities (DD group), and children from the general

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population (POP group). Children for the ASD and DD groups were identified from multiple special education and clinical sources that provide services to children with disabilities. Children recruited from each source were those with select special education or International Classification for Disease codes indicative of autism/ASD or other DDs often seen as precursor or co-occurring diagnoses in children eventually diagnosed with ASD. The POP group is composed of a random sample of children selected from birth certificates within a given site's defined geographic study area.

Recruitment, enrollment, and data collection activities for the first phase of SEED occurred from 2007 to 2012. Eligible children were born between 2003 and 2006, lived in the respective site's study area both at birth and at study enrollment, and lived with a caregiver since 6 months of age who could provide legal consent and was capable of communicating in English (all sites) or Spanish (two sites). Children were enrolled when they were 2–5 years of age. Across sites, 22% of the potential ASD or DD families who were contacted were found to be ineligible, 34% refused participation before eligibility could be determined, and 43% were eligible and enrolled. Among potential POP families contacted, 34% were known to be ineligible, 40% refused before eligibility could be determined, and 25% were eligible and enrolled.

Although children were initially identified as potentially being eligible for a given study group—ASD, DD, or POP— the final study group classification was determined from standardized research developmental assessments. Upon enrollment, all children were screened for possible autism characteristics through their caregiver's completion of the Social Communication Questionnaire (SCQ). Children with SCQ scores above a predetermined threshold (≥11) were designated as potential ASD cases regardless of how they were initially identified. Additionally, all children who had a previous ASD diagnosis or autism special education classification were designated as potential ASD cases regardless of their SCQ scores. Children in all study groups were seen in person as part of the study protocol and administered a developmental assessment. Children in the potential ASD group underwent a more comprehensive assessment than children in the other groups. In addition to a general developmental assessment, they were administered the Autism Diagnostic Observation Schedule (ADOS) and their caregivers were administered the Autism Diagnostic Interview revised (ADI-R). Final ASD case classification was based on the ADOS and ADI-R scores.

A wealth of data was collected from children in all study groups and their caregivers, including an extensive interview with the caregiver about family socio-demographics and, if the caregiver was the biological mother (98% of respondents), her reproductive history and information about her pregnancy with the index child.

Sample Selection

This analysis was focused on a comparison of children with a final classification of ASD versus POP (n = 1930). The DD group included a heterogeneous mix of children with different types of developmental delays and disabilities ranging from genetic syndromes to diagnoses of general developmental delays only. Because we did not have sufficient sample

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size to sub-divide the DD group into more meaningful analytic subgroups, we excluded them from the current analysis.

We excluded mother–child pairs missing data on infertility disorders and treatments (n = 273) or confounders (n = 13). We additionally excluded 106 mother–child pairs with maternal age <20 years and/or maternal education <12 years because within these demographic subgroups, both the ASD and POP study participants had very low occurrence (n = 0–5) of both infertility disorders and infertility treatments (thus, they were non-informative to this analysis). Our final sample included 1538 mother–child pairs: 629 ASD and 909 POP.

Infertility Exposures of Interest

We assessed two groups of exposures: (1) diagnosed infertility disorders; and (2) maternal treatments for infertility and/or to maintain pregnancy.

Infertility Disorders—The telephone interview with the child's mother included questions on whether before the index pregnancy a doctor or other healthcare provider ever told her it would be impossible or difficult to get pregnant—overall and because of specific infertility-related disorders, including blocked or damaged fallopian tubes; PCOS or multiple ovarian cysts; diminished ovarian reserve because of advanced age, premature ovarian failure or a medical condition; endometriosis; uterine problem, such as fibroids; or a diagnosis of unexplained infertility. Women could respond affirmatively to more than one disorder. Women were also given the option of describing verbatim an “other” reason they were told it was difficult to get pregnant. We systematically examined all “other” responses and, when possible, classified them into one or more of the aforementioned infertility-related disorder categories. We were conservative in our approach by distinguishing definite and possible diagnoses. That is, in some instances, we classified a woman's response as possibly, but not definitely being related to a certain type of infertility disorder, most notably possible PCOS or possible uterine problem. For these two disorders, we constructed two analytic “exposure” variables, one with a strict interpretation of “other” responses and one with a more liberal interpretation that included the possible classifications. We did not have sufficient sample size to separately examine mutually-exclusive reports of every infertility disorder and infertility disorder combination reported. However, we did examine more than one maternal infertility disorder as a separate exposure category.

Women were also asked a single question about male factor infertility—whether the child's biological father had ever been told prior to the index pregnancy that it would be difficult for him to father a child because of problems with his sperm.

Maternal Infertility Treatments—All maternal respondents, regardless of their responses to the infertility disorders questions, were asked whether they used any type of treatment or medication to help them get pregnant with the index pregnancy and/or maintain the pregnancy in the early stages. If they responded affirmatively, they were specifically asked about medications used, including a lengthy pre-specified list of medications and an option to provide the name of their medication(s) verbatim; assisted reproductive technology treatments (ARTs); assisted or artificial insemination; and surgery for an infertility condition

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within the 6 months preceding the index pregnancy. Women could respond affirmatively to more than one treatment. We systematically examined all medication, procedure, and surgery verbatim responses. In a few instances, we determined that a response did not meet criteria for an infertility treatment—examples included folic acid and Rhogam medications. However, most “other” responses corresponded with a valid type of infertility treatment.

We classified all medications reported into the following subtypes: ovarian stimulation-anti-estrogen; ovarian stimulation-gonadotropin; progesterone; human chorionic gonadotropin (hCG) and related; gonadotropin agonist/antagonist; other hormonal medication, such as estrogen; and other medication to prevent miscarriage, including anti-inflammatory medications and anticoagulants. Since many women used multiple treatments, we also created a mutually-exclusive hierarchy of treatments. Results were comparable when we considered each factor individually versus in a mutually-exclusive hierarchy; we therefore present only the former here.

Potential Confounders

We examined several demographic factors previously found to be associated with ASD diagnosis and ART use as potential confounders or effect modifiers. These included maternal race-ethnicity; maternal age, education and parity at index birth; and child sex. Because previous studies suggest preterm birth and/or multiple birth might be factors in the causal pathway between infertility treatments and ASD (Fountain et al. 2015; Sandin et al. 2013; Hvidtjorn et al. 2011; Klemetti et al. 2006), we also examined all analyses in sub-samples restricted to term births (≥37 weeks' gestation) and singleton births.

Child sex and maternal age were ascertained as part of the enrollment intake process. Maternal education, race-ethnicity, parity, and plurality were collected in the maternal telephone interview. Gestational age was provided in birth certificate files provided by each site for enrolled participants.

Statistical Analysis

In initial analyses, we examined percent distributions of all infertility disorders, infertility treatments and potential confounders by study group. We assessed statistical significance of differences with Chi square tests. We calculated crude and adjusted odds ratios (ORs, aORs) and corresponding 95% confidence intervals (CIs) for associations between ASD and each infertility disorder and each infertility treatment variable. Adjusted ORs were estimated from logistic regression models that included maternal age, education, and parity at index birth, maternal race-ethnicity, and child sex in addition to the infertility disorder/treatment of interest. We conducted stratified analyses to assess whether ORs varied substantially by any of the aforementioned potential confounders. We noted marked, consistent variation in aORs for several infertility disorder associations across parity strata. We therefore also present separate adjusted analyses of infertility disorders for children who were first births and second or later births.

To better understand the effect differences observed between infertility disorders and parity, we re-ran analyses of infertility disorders within two additional sub-samples of second or later births: (1) restriction to mother–child pairs in which none of the index child's older

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siblings had an ASD diagnoses; and (2) restriction to mother–child pairs in which the index pregnancy was not conceived after a short interval (<18 months) from the preceding birth. For this latter set of analyses, we separately examined subsets with an inter-pregnancy interval (IPI) of 18–59 months and an IPI of 60+ months. We did not combine these two groups because IPI of 60+ months has itself been found to be associated with ASD risk (Conde-Agudelo et al. 2016).

We also ran all of the models for associations with each infertility disorder and each infertility treatment in sub-samples restricted to term births and singleton births to assess whether preterm or multiple birth might be potential causal path factors.

Finally, we assessed the joint and separate effects of maternal infertility disorders and treatments in models that examined associations between ASD and (1) maternal infertility disorder (any type) but no maternal infertility treatment reported (any type); (2) maternal infertility treatment but no maternal infertility disorder reported; and (3) both maternal infertility disorder and treatment reported. We did not have sufficient sample size to assess individual disorders and treatments in this analysis series.

Results

Children with ASD were more likely than children in the POP sample to be male, a multiple birth, and born preterm (Table 1). Mothers of children with ASD were less likely than mothers of POP children to be NHW and have an advanced education at the time of their child's birth; they were also younger.

Infertility Disorders

In both unadjusted and adjusted analyses, we observed significant positive associations between ASD and diagnosis of maternal infertility generally, and diagnoses of blocked/damaged fallopian tubes, endometriosis, and uterine problems specifically; ORs and aORs ranged from 1.4 to 2.6 (Table 2). Stratified analyses indicated that these associations were limited to or much stronger in second or later births (aORs ranged from 1.9 to 6.3). Additionally, stratification revealed a significant association between ASD and PCOS and a nearly significant association between ASD and more than one maternal infertility disorder among second or later births (aORs ranged from 2.0 to 2.7). ASD was not associated with maternal diminished ovarian reserve or unexplained infertility. However, the effect estimates for unexplained infertility were imprecise due to low prevalence. ASD was also not associated with male-factor infertility.

The findings in Table 2 were similar in samples restricted to singletons and term births (Supplemental Table 1). In supplemental analyses of second or later births, we observed a similar pattern of results after excluding children from the sample who had an older sibling with an ASD diagnosis (a general indication of a possible genetic link to ASD) (Supplemental Table 2). We also observed a fairly similar pattern of results in subsets of second or later births conceived 18–59 months or 60+ months after the previous birth (Supplemental Table 2). However, all estimates were imprecise as evidenced by wide confidence intervals. While point estimates generally followed a similar pattern as that

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observed for the total sample of second or later births, a few associations appeared attenuated and others appeared strengthened. However, given the imprecision of estimates, those few departures from the general pattern might not be meaningful and thus, should be interpreted cautiously.

Treatment for Infertility or to Maintain Pregnancy

Although none of the findings were statistically significant, mothers of children with ASD were slightly more likely to have used an infertility treatment than mothers of POP children (Table 3). They had 20% higher odds of use of any maternal infertility treatment, and 20–50% higher odds of use of six of the nine specific infertility-related medications or procedures we examined: gonadotropin ovarian stimulation medications, progesterone medications, hCG medications; gonadotropin agonist/antagonist medications, other medications to prevent miscarriage, and ART. These findings are difficult to interpret, given case-control differences are modest and sample sizes for most treatments were low (<4% use in POP group for 5 of the 6 aforementioned treatments) and thus confidence intervals all included 1.0 both before and after adjustment. However, we note that the direction and magnitude of difference between cases and controls was consistent across treatments. Moreover, for all of the aforementioned treatments, aORs were attenuated in the sample restricted to singletons, and most were also attenuated in the sample restricted to term births.

Separate and Joint Effects Maternal Infertility Disorders and Treatments

Among 185 case mothers and 217 control mothers who reported either an infertility disorder or treatment, roughly one-third reported an infertility disorder only, one-third reported an infertility treatment only, and one-third reported both a disorder and a treatment. As observed for all infertility disorders together (Table 2), ASD was associated with both maternal infertility disorder with treatment and maternal infertility disorder without treatment in second or later births but not first births (Table 4). ASD was not associated with infertility treatment if a diagnosed infertility disorder had not been reported. Although sample size was too small for detailed analyses of individual disorders or treatments, we examined the types of infertility disorders reported by case and control mothers with and without treatment and the types of infertility/early pregnancy maintenance treatments reported by case and control mothers with and without a disorder (Supplemental Table 3). While some variability was observed, it was noteworthy that the full range of disorders was reported by case and control mothers regardless of whether they used a treatment for the index pregnancy. Likewise, the full range of treatments was reported for case and control mothers whether or not they reported a past infertility disorder diagnosis.

Discussion

Infertility Disorders

We document several positive associations between ASD and maternal infertility, including several specific diagnoses of infertility disorders. These associations varied by birth order (parity). While the magnitude of the aORs among second or later births was near or above 3.0 for four conditions (blocked tubes, PCOS, endometriosis, and uterine or related problems), indicating strong associations with ASD, aORs were markedly lower among first

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births. For two conditions (blocked tubes and PCOS), the findings were null among first births and for the other two conditions (endometriosis and uterine and related problems) aORs (1.8 and 1.6, respectively) were 45–71% lower among first births and the confidence intervals for these estimates overlapped 1.0.

These finding of differential effects by birth order were unexpected. Since multiparous women are more likely to be of advanced maternal age, we considered whether these findings reflected a maternal-age effect. However, our findings persisted after adjustment for maternal age as well as after adjustment for maternal education and race-ethnicity and child sex. Additionally, we ruled out multiple birth, preterm birth, short IPI, and possible genetic effects as underlying explanations for the parity differences. However, the estimates from our analyses restricted to children conceived at least 18 months after a previous birth were imprecise and thus, while the general pattern of results suggests infertility disorders remain a risk factor for ASD after removing the effect of short IPI, our sample was under-powered to examine this issue for many individual conditions. Additionally, we could not fully evaluate other potential explanations. For example, some studies indicate that endometriosis and uterine fibroids are associated with various pregnancy complications, including strong associations with placenta previa (Berlac et al. 2017; Parazzini et al. 2016) Placenta previa has been shown to occur more frequently in multiparous births (Ananth et al. 1996). We lacked data to examine this hypothesis. We also lacked data to examine whether infertility conditions were more severe or had been diagnosed later in women on their second or later birth than first birth.

Despite the remaining questions related to the effect modification by birth order, the consistency of our findings of positive associations across several infertility conditions potentially supports their validity. Moreover, an association between infertility disorders and ASD has biological plausibility. All four disorders we found to be associated with ASD have been linked to inflammation and various autoimmune conditions (Vannuccini et al. 2016; Tobias et al. 2015; Kes-kin Kurt et al. 2014; Bungum et al. 2014; Kobayashi et al. 2014; Ott et al. 2014; Kachuei et al. 2012; Horne and Critchley 2007; Confino and Radwanska 1992). Inflammation and auto-immunity have been implicated in ASD etiology as well (Ornoy et al. 2016). Additionally, the defining feature of PCOS is a hormonal imbalance and research suggests a relationship between prenatal androgen levels and autistic traits (Wen and Wen 2014).

Few previous studies have assessed associations between ASD and infertility conditions and none have conducted as in depth analyses, including detailed stratified analyses of specific infertility conditions, as the current study. A case-control study of children born 1995–1998 who were included in a healthcare organization database reported that mothers of case children were significantly more likely than mothers of control children to have a history of infertility prior to conception, to have sought an evaluation in an infertility specialty clinic, and to have received an infertility diagnosis (Grether et al. 2013). These associations were attenuated and no longer statistically significant after restriction to singleton births, which might suggest that some of the effect was explained by infertility treatments (which pose a high risk for multiple birth); however, none of the infertility treatments assessed by the authors were associated with ASD. This study was limited in that data regarding specific

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infertility conditions were not presented. A second case-control study of children residing in several regions in California reported similar proportions of maternal or paternal infertility diagnoses for children with ASD and typically-developing control children (Lyall et al. 2013); however, specific infertility conditions could not be fully assessed because of very small numbers of both case and control mothers reporting individual infertility conditions. A third study, using a nested case-control design drawn from the Nurse's Health Study (NHS), which had a larger sample to assess individual conditions, also reported no association between infertility conditions and ASD (Lyall et al. 2012). There were notable differences between this study and the current study, particularly in the ascertainment of infertility. The NHS infertility question series was more restrictive than the SEED infertility question series in that women were only asked about specific infertility causes if they first responded affirmatively to a question on whether they had tried to become pregnant for more than a year without success. SEED did not place this type of sequential “rule-out” criterion on women, which might have had a notable impact on ascertainment. Not all women will wait 1 year before seeking an infertility assessment, particularly those of advanced age and those diagnosed with an infertility disorder prior to trying to become pregnant (i.e. those who had previously sought a diagnostic work up at young ages in response to symptomatology). The SEED questions were also more specific than NHS in that they asked women to report infertility-related conditions diagnosed by a doctor or other healthcare provider, while NHS question verbiage simply asked the woman to report the reason (cause) she had difficulty becoming pregnant. Also, in contrast to NHS, the SEED questions included explanatory descriptions for some conditions as part of the question verbiage, the instrument was administered via phone by trained interviewers who were provided definitions for all conditions such that they could answer participant questions, and the instrument allowed for verbatim reporting of “other” conditions. These “other” responses were systematically reviewed and coded for this study. Finally, NHS includes a very select segment of the population—registered nurses from select states— who likely differ from the general US population on various health conditions and healthcare seeking behavior. In contrast to the studies reporting null findings, two previous studies that examined the association between ASD or ASD symptoms and a single condition—maternal PCOS— reported positive associations (Kosidou et al. 2015; Palomba et al. 2012).

Treatment for Infertility or to Maintain Pregnancy

Although we observed that a slightly higher proportion of mothers of children with ASD than mothers of POP children had used a treatment to help them become pregnant or maintain their pregnancy, these findings were attenuated after restricting the sample to singleton births. Most effect estimates were also attenuated after restriction to term births. While none of our findings reached statistical significance, the findings of a modest effect overall with attenuation after restriction to singletons was consistent across the majority of treatments we examined in this study. Moreover, both the magnitude and attenuation of effects that we observed are consistent with most other previous large studies of the relationship between ASD and ART (Fountain et al. 2015; Sandin et al. 2013; Hvidtjorn et al. 2011; Klemetti et al. 2006). Thus, our findings support previous studies suggesting that maternal infertility treatments such as ART may be linked to ASD by increasing risk of multiple birth, or preterm birth.

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Few studies have examined non-ART infertility treatments. One study reported no differences between ASD cases and typically developing controls in either ART use or use of various non-ART infertility treatments (Lyall et al. 2013). Two other studies reported positive associations between use of non-ART ovulation induction medications and ASD, findings that were particularly noteworthy in that neither observed associations with ART, a treatment that nearly always includes high doses of ovulation induction medications (Lyall et al. 2012; Hvidtjorn et al. 2011). Those potentially paradoxical findings might suggest that the ASD-ovulation induction associations reported in those studies are not causal, but rather are related to a woman's underlying infertility status. This hypothesis is possibly supported by subgroup analyses in one study (Lyall et al. 2012), which revealed that the ASD-ovulation induction medications association was limited to women of advanced maternal age. The authors posit that ovulation induction might have stimulated the release of “sub-optimal” oocytes more often in older rather than younger women. Nonetheless, no definitive conclusions about the underlying reason for the observed ASD-ovulation induction association can be drawn based on the data presented in either study and a direct relationship cannot be ruled out. Given the limited study of non-ART infertility treatments to date, further study is warranted.

Separate and Joint Effects Maternal Infertility Disorders and Treatments

Our findings of the combined infertility disorder-infertility treatment variables substantiate our findings from our separate analyses of disorders and treatments. Receipt of an infertility-related treatment without a prior infertility diagnosis was not associated with ASD, while having a past diagnosis of an infertility disorder was associated with ASD whether or not the woman had received a treatment just prior to or early in the index pregnancy. We did not collect information on the specific reasons women used an infertility or early pregnancy maintenance treatment for the index pregnancy, but in practice there is a wide variation in how long women try to conceive a pregnancy naturally prior to seeking help in becoming pregnant, and some women may be started on a course of treatment without first undergoing a full diagnostic work-up. Additionally, various treatments are used to achieve pregnancy for social reasons (i.e. single mothers) in addition to infertility reasons.

Study Limitations

The findings presented here must be interpreted in the context of several limitations. Even though our sample size included more than 600 children with ASD and more than 900 population controls, it was not sufficient to examine several important subgroups, including ASD case subtypes, which might be etiologically distinct; nor was it sufficient to examine meaningful subgroups of the heterogeneous DD group enrolled in SEED. Future analyses that incorporate data from subsequent phases of SEED will be valuable in continuing to explore the relationships described here in both ASD and DD subgroups. Additionally, the findings presented here for individual infertility disorders and treatments should be interpreted cautiously, given small numbers of exposed cases and controls in some analyses.

Maternal infertility disorders and treatments were reported 3–5 years postpartum and thus, it is important to consider whether recall bias may have influenced our findings. Recall bias is most likely for factors for which: (1) recall is difficult generally; and (2) the respondent

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believes the factor might be a contributor to the condition of interest (Grimes and Schulz 2002; Coughlin 1990). In SEED, respondents were asked to recall infertility disorders that had been diagnosed by a healthcare provider. Women who obtain diagnoses of specific infertility conditions are those who either had difficulty conceiving a pregnancy and sought a medical evaluation or sought help for symptoms for a condition such as uterine fibroids or endometriosis. Thus, infertility disorder diagnoses should be fairly salient events. While we did not have data to directly assess the validity of maternally-reported infertility conditions or treatments, the findings from previous studies are generally reassuring. Barradas and colleagues (2012) found that estimates of maternally-reported ART use from the population-based Pregnancy Risk Assessment Monitoring System were similar to estimates derived from ART provider reports to the National ART Surveillance System. De Boer and colleagues (2005) reported excellent specificity for self-reported infertility among a Dutch cohort of women who previously underwent ART (range 89–96% for specific types of infertility). Sensitivities were also moderate to good (65–84%) for tubal-factor infertility, male-factor infertility, hormonal infertility, and endometriosis; however, the sensitivity for uterine factor infertility was lower (46%), indicating uterine-factor might not be as salient of a diagnosis, especially in women with multiple types of infertility. Nonetheless, even if some under-reporting of infertility diagnoses occurred, it is unlikely that it was related to case status. While we cannot definitively rule out that respondents believed their infertility condition was the cause of their child's autism, the infertility disorder questions were a small part of a lengthy maternal interview which included questions on many pregnancy behaviors and exposures which would likely have been more concerning to women; thus, the infertility questions should not have stood out.

In contrast to many other ASD studies, SEED sought to enroll a diverse population-based sample by identifying potentially eligible case children from multiple clinical and education sources serving children throughout each site's catchment area and identifying potential control children from birth certificate samples. One drawback to this approach is that numerous families targeted for potential recruitment could not be located or contacted. It is likely that many of these families were actually ineligible for inclusion since our a priori eligibility criteria required children to have current as well as birth residence in the study catchment area; four sites also required parents to be able to communicate well in English. Given the low response rate, selection bias should be considered. In a separate study (currently unpublished) we conducted a detailed analysis to assess whether non-response was likely to have resulted in selection bias by assessing various risk estimates using data from one site that had access to some data on all families initially invited. We found that associations between ASD and several perinatal factors, such as preterm birth, were comparable between the final sample of enrolled participants who completed the study and the full sample of invited participants (unpublished data). Moreover, that study assessed select associations of maternally-reported factors, including maternal report of an infertility disorder, after weighting the final sample to align demographically with the initial invited sample of participants; no notable differences were observed in the findings from the weighted and unweighted (original) analyses.

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Study Strengths

Despite potential limitations, the SEED sample had many strengths, including comprehensive case classification methodology using instruments considered gold-standards for ASD diagnoses and detailed exposure ascertainment that allowed us to conduct a much more comprehensive analysis than other studies to date. Additionally, SEED recruitment methods resulted in a diverse group of both case and control children. And SEED was intentionally designed to identify children with undiagnosed ASD, which is likely more common in underserved segments of the population. Finally, while our sample size was not sufficient to examine all subgroup analyses of interest, it was nonetheless one of the largest studies to date with detailed data on a range of infertility treatments and disorders and intensive standardized identification and classification of ASD.

Conclusion

Our findings suggest maternal infertility disorders are associated with ASD. In our sample, this effect was limited to second or later births, but mechanisms for this effect modification are not apparent and need to be explored further. While infertility treatments appeared to be modestly associated with ASD in initial analyses, no associations between ASD and infertility treatments were observed in analyses restricted to singleton births. Further study will be important to more fully characterize the associations reported here and to explore mediation mechanisms that may be in play, with the ultimate goal being to fully inform women who have been diagnosed with these disorders of the potential risks of these disorders and their treatment so as to minimize adverse child neurodevelopment outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Table 1

Demographic, pregnancy, and birth characteristics of study population according to case-control group, Study to Explore Early Development

	ASD (N = 629) %	POP (N = 909) %	p value
Child sex			<0.0001
Male	82.5	53.8	
Female	17.5	46.2	
Parity of index birth			0.1121
First birth	48.3	44.2	
Second or later birth	51.7	55.8	
Maternal race-ethnicity			<0.0001
Non-Hispanic white	59.0	73.9	
Non-white and/or Hispanic	41.0	26.1	
Maternal age at birth (years)			0.0080
20–34	70.3	68.9	
35+	29.7	31.1	
Maternal education at birth (years completed)			<0.0001
12	14.2	8.3	
13–15	30.5	23.8	
16+	55.3	68.0	
Birth plurality			
Singleton	91.7	96.3	0.0001
Multiple	8.3	3.7	
Gestational age			<0.0001
Term, 37+ weeks	83.6	90.8	
Preterm, <37 weeks	16.4	9.2	

ASD autism spectrum disorder case group, *POP* population control group

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Table 2

Associations between autism spectrum disorder and maternal or paternal infertility disorders, Study to Explore Early Development

Infertility disorder[a]	ASD (N = 629) N (%)	POP (N = 909) N (%)	Total sample Unadj. OR (95% CI)	Total sample aOR[b] (95% CI)	First birth aOR (95% CI)	Second or later birth aOR (95% CI)
Any maternal infertility disorder[c]	124 (19.7)	138 (15.2)	1.4 (1.1–1.8)	1.4 (1.1–1.9)	1.1 (0.7–1.7)	1.9 (1.3–2.9)
Blocked or damaged tubes	20 (3.2)	13 (1.4)	2.3 (1.1–4.6)	2.2 (1.0–4.7)	1.2 (0.3-4.0)	3.4 (1.3–9.3)
PCOS/multiple ovarian cysts	33 (5.3)	46 (5.1)	1.0 (0.7–1.6)	1.0 (0.6–1.7)	0.6 (0.3–1.1)	2.7 (1.2–6.1)
PCOS/multiple ovarian cysts or related symptoms reported[d]	47 (7.5)	71 (7.8)	0.9 (0.7–1.4)	1.1 (0.7–1.6)	0.7 (0.4–1.2)	2.0 (1.1–3.8)
Diminished ovarian reserve[e]	16 (2.5)	18 (2.0)	1.3 (0.7–2.6)	1.2 (0.6–2.6)	1.1 (0.4–3.0)	1.3 (0.4–4.0)
Endometriosis	27 (4.3)	19 (2.1)	2.1 (1.2–3.8)	2.5 (1.3–4.7)	1.8 (0.8–4.7)	3.3 (1.3–8.3)
Uterine problem (e.g. fbroids)	30 (4.8)	18 (2.0)	2.5 (1.4–4.5)	2.4 (1.3–4.5)	1.3 (0.6–3.1)	6.3 (2.2–18.5)
Uterine problem or related problem or diagnosis reported[f]	39 (6.2)	23 (2.5)	2.5 (1.5–4.3)	2.6 (1.4–4.5)	1.6 (0.7–3.4)	5.3 (2.2–12.9)
Unexplained infertility	11 (1.8)	11 (1.2)	1.5 (0.6–3.4)	1.5 (0.6–3.8)	3.3 (0.6–18.6)	1.0 (0.3–3.2)
More than one maternal infertility disorder	68 (10.8)	66 (7.3)	1.4 (0.8–2.3)	1.2 (0.6–2.1)	0.6 (0.3–1.5)	2.4 (0.97–5.9)
Male factor infertility	34 (5.4)	40 (4.4)	1.2 (0.8–2.0)	1.1 (0.7–1.9)	1.1 (0.6–2.1)	1.1 (0.5–2.4)

ASD autism spectrum disorder case group, *POP* population control group, *PCOS* polycystic ovarian syndrome

[a] Specific infertility disorders not mutually exclusive

[b] aOR: odds ratio for total sample adjusted for maternal age at birth, maternal education at birth, maternal race-ethnicity, child sex, and parity; odds ratios for first birth and second or later birth adjusted for the same factors with the exception of parity

[c] 10 cases and 9 controls with a report of maternal infertility are not further classified within one of the specific types listed on the table because data were missing for the specific type or the verbatim description did not contain sufficient information to allow for classification into one of the maternal infertility disorder types

[d] PCOS/multiple ovarian cysts or related symptoms includes PCOS/multiple ovarian cysts diagnoses + cases without a clear diagnosis mentioned, but healthcare provider noted symptoms consistent with PCOS were related to infertility problems (e.g. overweight associated with ovulation problems)

[e] Diminished ovarian reserve includes premature ovarian failure and infertility related to age, chronic disease, or eating disorder

[f] Uterine problem or related problem or diagnosis includes uterine problem diagnoses (such as fibroids) + infertility related to maternal diethyl-stilbestrol (DES) exposure, infertility secondary to chromosomal defect, infertility associated with cervical issues, and infertility related to problems with progesterone

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Table 3

Associations between autism spectrum disorder and maternal use of treatments to help become pregnant or maintain pregnancy, Study to Explore Early Development

Treatment[a]	ASD (N = 629) N (%)	POP (N = 909) N (%)	Total sample Unadj. OR (95% CI)	Total sample aOR[b] (95% CI)	Term births aOR (95% CI)	Singletons aOR (95% CI)
Any maternal infertility treatment	121 (19.2)	152 (16.7)	1.2 (0.9–1.5)	1.2 (0.9–1.5)	1.0 (0.8–1.4)	1.0 (0.7–1.4)
Any maternal surgery infertility condition	34 (5.4)	49 (5.4)	1.0 (0.6–1.6)	0.9 (0.6–1.5)	0.9 (0.5–1.6)	0.7 (0.4–1.3)
Any medication—miscarriage or infertility	108 (17.2)	131 (14.4)	1.2 (0.9–1.6)	1.3 (0.9–1.7)	1.1 (0.8–1.6)	1.1 (0.8–1.5)
Medication type						
Ovarian stimulation—anti-estrogens	34 (5.4)	49 (5.4)	1.0 (0.6–1.6)	1.1 (0.7–1.8)	0.8 (0.4–1.4)	0.8 (0.5–1.5)
Ovarian stimulation—gonado-tropins	30 (4.8)	33 (3.6)	1.3 (0.8–2.2)	1.4 (0.8–2.4)	1.1 (0.5–2.2)	0.8 (0.4–1.7)
Progesterone	66 (10.5)	82 (9.0)	1.2 (0.8–1.7)	1.3 (0.9–1.8)	1.2 (0.8–1.9)	1.1 (0.7–1.7)
Human chorionic gonadotropin	26 (4.1)	30 (3.3)	1.3 (0.7–2.2)	1.3 (0.7–2.2)	1.0 (0.5–2.2)	0.8 (0.4–1.7)
Gonadotropin agonist/antagonist	19 (3.0)	18(2.0)	1.5 (0.8–3.0)	1.8 (0.9–3.7)	1.9 (0.8–4.8)	0.9 (0.3–2.3)
Other hormonal medications, such as estrogen	8 (1.3)	11 (1.2)	1.1 (0.4–2.6)	1.1 (0.4–3.0)	1.5 (0.5–4.6)	0.9 (0.2–3.5)
Other medications to prevent miscarriage (anticoagulants, anti-infamma-tory, etc.)	25 (4.0)	30 (3.3)	1.2 (0.7–2.1)	1.3 (0.7–2.3)	1.0 (0.5–2.0)	0.9 (0.4–1.8)
Infertility treatment procedures Assisted insemination	17 (2.7)	25 (2.8)	1.0 (0.5–1.8)	1.0 (0.5–1.9)	0.9 (0.4–1.9)	0.9 (0.4–2.0)
Assistive reproductive technology	26 (4.1)	30 (3.3)	1.3 (0.7–2.2)	1.3 (0.7–2.4)	1.5 (0.7–3.2)	0.6 (0.2–1.8)

ASD autism spectrum disorder case group, *POP* population control group

[a] Treatments are not mutually-exclusive

[b] aOR: odds ratios adjusted for maternal age at birth, maternal education at birth, maternal race-ethnicity, parity of index birth, and child sex

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Table 4

Assessment of separate and joint effects of maternal infertility disorders and treatments, Study to Explore Early Development

	ASD (N = 629) N (%)	POP (N = 909) N (%)	Total sample Unadj. OR (95% CI)	Total sample aOR[a] (95% CI)	First birth aOR (95% CI)	Second or later birth aOR (95% CI)
Infertility disorder, NO treatment	64 (10.2)	65 (7.2)	1.5 (1.02–2.1)	1.6 (1.1–2.4)	1.4 (0.8–2.5)	1.9 (1.1–3.3)
Infertility treatment, NO disorder	61 (9.8)	79 (8.7)	1.1 (0.8–1.6)	1.1 (0.8–1.6)	1.4 (0.8–2.4)	0.8 (0.5–1.5)
Infertility disorder and treatment	60 (9.5)	73 (8.1)	1.2 (0.8–1.7)	1.2 (0.8–1.7)	0.9 (0.5–1.5)	1.7 (0.9–3.1)

ASD autism spectrum disorder case group, *POP* population control group

[a]aOR: odds ratios adjusted for maternal age at birth, maternal education at birth, maternal race-ethnicity, parity of index birth, and child sex; odds ratios for first birth and second or later birth adjusted for the same factors with the exception of parity